UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,522	05/02/2002	Marc G. Jacquemin	522-1769	5981

7590 05/20/2004

William M Lee Jr
Lee Mann Smith McWilliams
Sweeney & Ohlson
PO Box 2786
Chicago, IL 60690-2786

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,522	JACQUEMIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-30,32-36 and 38-47* is/are pending in the application.

4a) Of the above claim(s) *44-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,32-36 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/13/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 27-30, 32-36 and 38-47 are pending.

2. Applicant's election with traverse of Group I, claims 27-30, 32-36 and 38-43 drawn to a monoclonal antibody against factor VIII, a cell line, fragments, and a composition thereof filed on 4/5/04, is acknowledged.

Applicant traverses the restriction requirement but contends that there is insufficient time to responds in the one month allotted and that applicant reserve any further comments to when the examiner issues a substantive office action. The Examiner will consider Applicant's response upon receiving the arguments.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 44-47 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 28-30, 32-36 and 38-43 are under as they read on a monoclonal antibody against factor VIII, a cell line, fragments, and a composition thereof.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 27-30, 32-36 and 38-43are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitation "by binding to a site of the said factor or complex" in claims 28-29 and 34-35 is ambiguous and indefinite because the claimed monoclonal antibody recognizes an epitope located in C1 domain of factor VIII. Therefore, it is unclear how such antibody would bind to a site of factor VIII or even to the complex.

B. The recitation "by on purpose immunization in animals" in claim 32 " and being humanized" in claim 33 is ambiguous. It is unclear what is being claimed. The claims appear to be incomplete and omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the product being immunized and the method of obtaining the monoclonal antibody by immunizing the animal with the product. Further, the humanization of the monoclonal antibody does not require the immunization steps.

C. It is improper to recite "monoclonal antibodies" in claims 38 and 39 as the claims should recite the singular form. It is suggested that the word be changed to "a monoclonal antibody".

7. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 28-30 and 32-33 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 28-30 and 32-33, as written, do not sufficiently distinguish over cells and antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Purified" as disclosed on page 21, lines 14 and 35 of specification. See MPEP 2105.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the cell line KRIX 1 that produce the fVIII C1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of*

the patent whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

10. Claims 28-30, 32-36 and 38-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which specifically binds C1 domain of factor VIII, does not reasonably provide enablement for any monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of "at least 65% and at most 98%" inactivating factor VIII or a complex of two or "more factors" involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a side of the said factor or complex in claim 28, or a cell line producing a human monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or "more factors" involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a site of the said factor or complex in claim 29, "being produced by on purpose immunization in animals in claim 32, being produced by on purpose immunization in animals and being humanized in claim 33, any comlementarity determining region, any soluble or membrane-anchored single-chain variable part, any single variable domain or any derivative of any monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or "more factors involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a site of the said factor or complex in claim 34, or a pharmaceutical composition for the prevention or treatment of disorders of hemostasis and resulting pathologic conditions in mammals, comprising as an active ingredient a monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or "more" factors involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a site of the said factor or complex, or any "fragment, derivative or homolog thereof" in admixture with a pharmaceutically acceptable carrier in claim 35, or a method of obtaining monoclonal antibodies from a non-human mammal, comprising the steps of a) selecting a non-human mammal having a "modified and partially functional protein" the modification being with respect to a wild type protein and lying in a domain of the protein, administering the wild type protein to the non-human mammal in order to elicit an immune response and selecting B-lymphocytes from the non-human mammal which produce antibodies which only partially inactivate the wild type protein in claim 38, a method of obtaining monoclonal antibodies from the blood of a human being having modified and partially functional protein, the modification being with respect to a wild type protein and lying in a domain of the protein, and to whom the wild type protein was administered, the said method comprising the step of selecting, from the blood of said human being, B-lymphocytes which produce antibodies which only partially inactivate the wild type protein in claim 39. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Beside, the human monoclonal antibody secreted by KRIX 1 hybridoma and anti-fVIII C1 domain antibody, Applicant has not provided sufficient biochemical information that distinctly identifies such "having the capacity of at least 65% and at most 98% inactivating factor VIII". In addition to von Willebrand factor complex the specification fails to identify any "complex of two or more factors involving factor VIII". Furthermore, the specification does not reasonably provide enablement for any complementarity determining region, a soluble or membrane-anchored single-chain part, a single variable domain or a derivative of a monoclonal antibody being able to recognized an epitope located in the C1 domain of fVIII. Neither does the specification provide sufficient enablement for monoclonal antibody the bind to a site of fVIII or complex or a fragment, derivative or homolog of fVIII. There is insufficient guidance in the specification for the claimed method of obtaining the monoclonal antibodies. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. There is insufficient direction or objective evidence as to how to make and to how to use such antibodies. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The specification on page 10, lines 33-34 and page 11, under fig 3 discloses that the anti-fVIII antibodies such as KRIX 1 inhibit factor VIII activity by no more than 85% when used in access. Thus, the specification fails to disclose any antibodies that recognize an epitope located in the C1 domain of fVIII and having the capacity of at least 65% and at most 98% inactivating factor VIII and a complex of two or more factors involving factor VIII. Further the specification on page 4, lines 32-38 discloses that the type II polyclonal antibody inhibitors have partial capacity to inhibit fVIII which is believed to be due to a steric effect of von Willebrand factor. Further the specification on page 11, discloses that type II inhibitors react with different antigenic determinants than type I antibodies and that these determinants are partially blocking in the factor VIII/von Willebrand factor complex. The specification fails to provide an antibody that inactivate factor VIII or any complex of two or more factors involving factor VIII.

Also, at issue is whether or not the claimed composition of claim 35 would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Further at issue is the claimed CDR, the soluble or membrane-anchored single-chain variable part, the single variable domain or the derivative of the monoclonal antibody. The claims as written does not even require that such fragments/derivative to bind fVIII C1 but be part of the any monoclonal antibody that binds to fVIII C1. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. The specification fails to provide guidance regarding which CDR, single chain variable part, single variable domain or derivative of the monoclonal antibody would result in an antigen-binding fragment that being able to recognize an epitope located in the C1 domain of factor VIII. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of variants where the expectation of retaining similar function is unpredictable based on the instant disclosure.

Claim 35 recites that the antibody binds to a site of the said factor or complex or a fragment derivative or homolog thereof, however the specification fails to provide any fragment of fVIII C1 or derivative or homolog thereof. The specification does not even point out where does fVIII C1 domain starts and ends. No derivative has been disclosed for the skilled artisan to practice the claimed invention. Similarly, claims 38-39 recite "having a modified and partially functional protein", however, the specification only discloses only obtaining B lymphocytes from hemophilic A patients but disclose nothing about the modified and partially functional protein beside a definition. Example 2 on page 22 refers back to example 1 but says nothing regarding the modified protein. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and positions within the protein's sequence where amino acid modifications can be made with a reasonable expectations of success in obtaining similar biological or pharmaceutical activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. Without sufficient guidance, the changes which can be made in the structure of the C1 domain and still results in acquired hemophilia is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 28-30, 32-36 and 38-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody which specifically binds C1 domain of factor VIII.

Applicant is not in possession of any monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of "at least 65% and at most 98%" inactivating factor VIII or a complex of two or "more factors" involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a side of the said factor or complex in claim 28, or a cell line producing a human monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or "more factors" involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a site of the said factor or complex in claim 29, "being produced by on purpose immunization in animals in claim 32, being produced by on purpose immunization in animals and being humanized in claim 33, any comlementarity determining region, any soluble or membrane-anchored single-chain variable part, any single variable domain or any derivative of any monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or "more factors involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a site of the said factor or complex in claim 34, or a pharmaceutical composition for the prevention or treatment of disorders of hemostasis and resulting pathologic conditions in mammals, comprising as an active ingredient a monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII and having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or "more" factors involving factor VIII when the said monoclonal antibody is in a physiological excess by binding to a site of the said factor or complex, or any "fragment, derivative or homolog thereof" in admixture with a pharmaceutically acceptable carrier in claim 35, or a method of obtaining monoclonal antibodies from a non-human mammal, comprising the steps of a) selecting a non-human mammal having a "modified and partially functional protein" the modification being with respect to a wild type protein and lying in a domain of the protein, administering the wild type protein to the non-human mammal in order to elicit an immune response and selecting B-lymphocytes from the non-human mammal which produce antibodies which only partially inactivate the wild type protein in claim 38, a method of obtaining monoclonal antibodies from the blood of a human being having modified and partially functional protein, the modification being with respect to a wild type protein and lying in a domain of the protein, and to whom the wild type protein was administered, the said method comprising the step of selecting, from the blood of said human being, B-lymphocytes which produce antibodies which only partially inactivate the wild type protein in claim 39.

Applicant has disclosed only anti-fVIII C1 antibody having no more than 85% inactivation to fVIII ; therefore, the skilled artisan cannot envision all the contemplated monoclonal antibody possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 28-30, 32-33, and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenting et al (J Biol. Chem, 269:7150-7165, 1994) (of record).

Lenting *et al* teach a monoclonal antibody, CLB-CAg 12, specific for factor VIII-LC which comprises C1 domain (see page 7150, under Antibodies, in particular). Lenting *et al* teach that CLB-CAg 12 is non-inhibitory (with respect to FIXa) and binds to unidentified FVIII (see page 7151, last paragraph in particular). Finally, Lenting et al teach that the antibody in 1 M NaCl, 1%

Has, 25mM Tris (see page 7151 under protein concentration in particular) which is also consider to be a pharmaceutically acceptable carrier. While the prior art teachings may be silent as to the "having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or more factors involving factor VIII" per se; the reference product is the same as the claimed product. Therefore "having the capacity of at least 65% and at most 98% inactivating factor VIII or a complex of two or more factors involving factor VIII" is considered inherent properties.

Claims 32-33 are included because an antibody is same antibody irrespective of how it is made.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not have the capacity of at least 65% and at most 98% inactivating factor VIII recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

14. Claims 39-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacquemin et al (Blood. 1998 Jul 15;92(2):496-506) (IDS Ref).

Jacquemin *et al* a method of obtaining monoclonal antibodies from a hemophilia A patient (BO) (having a modified and partially functional fVIII protein) with inhibitor to fVIII Jacquemin et al teach that the hemophilia A patients received fVIII infusions (wild-type) (see Abstract and page 503, under Discussion in particular). Peripheral blood mononuclear cells were prepared by Ficoll-Hypaque density centrifugation using standard methods (see page 497, under Peripheral Blood Lymphocytes and cell lines in particular). Jacquemin et al further teach that PBMCs were immortalized using Epstein-Barr virus (EBV) supernatant (B95-8 strain). Culture supernatants were tested in enzyme-linked immunosorbent assay (ELISA) for the presence of anti-fVIII antibodies. Positive cell lines were cloned (see page 497, under Immortalization of Human PBMCs and page 499 under Results in particular).

The reference teachings anticipate the claimed invention.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 28-30, 32-33, 35-36 and 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peerlinck et al. Blood. 93(7):2267-2273, April 1999) or Gilles et al 1998 each in view of U.S. Patent No. 6,602,015.

Peerlinck et al teach a polyclonal antibody prepared from a LE patient with mild hemophilia A, inhibited the activity of allogeneic (wild-type) but not of self FVIII which contain Arg2150His mutation (see page 2267 under abstract) and that the kinetics of FVIII inhibition follwed a type II pattern. Further, Peerlinck et al teach that the polyclonal LE IgG recognized the FVIII light chain in enzyme-linked immunosorbent assay and the recombinant A3-C1 domains in an immunoprecipitation assay, indicating that at least part of LE antibodies reacted with the FVIII domain encompassing the mutation site (i.e., C1 domain). Peerlinck et al teach that the epitope(s) of LE IgG recocognized by LE IgG is located in A3-C1 and the epitope(s) is located at or close to the mutation site (i.e. Arg2150) (see page 2272, 1st col., Peerlinck et al teach that the LE igG inhibited FVIII activity by decreasing the rate of FVIIIa release from vWF, but LE IgG recognized an epitope distinct from ESH8 monoclonal antibody (i.e., residues 2248-2285 in the C2 domain) (see the abstract in particular). Peerlinck et al teach that the binding of patient LE IgG to insolubilized rFVIII was inhibited by more than 90% when LE igG were preincubated with the isolated FVIII light chain (see page 2271, 1st col., and Table 1 in particular). Peerlinck et al teach the LE IgG in 50 µl at 18 mg/ml concentration, that means that the antibody is in solution which is also consider to be a pharmaceutically acceptable carrier. Furthermore, Peerlinck et al teaches isolated rFVIII light chain (see page 2267 under Reagents and Buffers in particular). Further, the LE IgG inactivated FVIII was related to an antibody-dependent reduction in the dissociation from vWF. Peerlinck et al further teach that the LE patient was diagnosed with mild hemophila A with Arg2150His mutation in the factor VIII(FVIII) and that LE patient received FVIII infusions (see page 2268 under patient histories in particular).

Gilles et al teach a polyclonal anti-FVIII antibodies obtained form a mild hemophilia A patient (LE) with an Arg2150His mutation in the C1 domain. The anti-FVIII antibodies were shown to inhibit allogeneic but not self FVIII. Further, the inhibitory activity of such antibodies was much increased in presence of vWF. Gilles et al teach that the data indicated that a clinically-relevant FVIII B cell epitope generated by the association of FVIII with vWF is lost on the Arg2150His FVIII molecule. Gilles et al teach this point mutation in the FVIII light chain offers the first example of clinically-relevant FVIII B cell epitope(s) generated by the association of FVIII with

vWF (see abstract). Gilles et al teach the use of antibody in different assays which requires the antibodies to be in solutions.

Claims 32-33 are included because an antibody is same antibody irrespective of how it is made.

The claimed invention differs from the reference teachings only by the recitation of a monoclonal antibody in claims 28, 30, 32-33, a cell line in claim 29, selecting B-lymphocytes form the human being, B-Lymphocytes in claims 38-39.

The `015 patent teaches the autoantibodies are polyclonal antibodies and that monoclonal antibodies are prepared by isolating lymphocytes from the so-identified animals, producing a plurality of hybridomas from the lymphocytes and screening the monoclaonal antibodies produced by the hybridomas to identify monoclaonal antibodies (col. 2, lines 61-66 in particular). The `015 patent teaches that peripheral blood lymphocytes of an animal identified as having rate enhancing autoantibodies for a particular substrate can be stimulated to grow in culture and, therefore, can be immortalized using methodologies well known in the art. For example, the lymphocytes can be so stimulated using a virus, a chemical agent or a nucleic acid (e.g., an oncogene). A particularly advantageous virus for immortalization is Epstein Barr virus (EBV). Thus, rate enhancing autoantibodies can be produced by the transformed cells. The so transformed cells can then be cloned using known methods to provide a reliable source of large amounts of monoclonal antibodies having rate enhancing activity for a given substrate the transformed cells can then be cloned using known methods to provide a reliable source of large amounts of monoclonal antibodies (col., 8, lines 34-45 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the autoantibodies taught by Peerlinck et al or Gilles et al a monoclonal antibodies using the method taught by the `015 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such a method would provide a reliable source of large amounts of monoclonal antibodies as taught by `015 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peerlinck et al or Gilles each in view of U.S. Patent No. 6,602,015, as applied to claims 28-30, 32-33, 35-36, and 38-43 and further in view of Owens *et al* (1994).

The teachings of Peerlinck et al and Gilles references and `015 patent have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody in claim 34.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the autoantibodies taught by Peerlinck et al or Gilles as a monoclonal antibodies as taught by Owens et al and further obtain a humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jacquemin et al (Blood. 1998 Jul 15;92(2):496-506) (IDS Ref) in view of U.S. Patent No. 6,602,015.

The teachings of Jacquemin *et al* reference and `015 patent have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a non-human mammal in claim 38.

The `015 patent teaches the autoantibodies are polyclonal antibodies and that monoclonal antibodies are prepared by isolating lymphocytes from the so-identified animals, producing a plurality of hybridomas from the lymphocytes and screening the monoclaonal antibodies

produced by the hybridomas to identify monoclaonal antibodies (col. 2, lines 61-66 in particular). The `015 patent teaches that peripheral blood lymphocytes of an animal identified as having rate enhancing autoantibodies for a particular substrate can be stimulated to grow in culture and, therefore, can be immortalized using methodologies well known in the art. For example, the lymphocytes can be so stimulated using a virus, a chemical agent or a nucleic acid (e.g., an oncogene). A particularly advantageous virus for immortalization is Epstein Barr virus (EBV). Thus, rate enhancing autoantibodies can be produced by the transformed cells. The so transformed cells can then be cloned using known methods to provide a reliable source of large amounts of monoclonal antibodies having rate enhancing activity for a given substrate the transformed cells can then be cloned using known methods to provide a reliable source of large amounts of monoclonal antibodies (col., 8, lines 34-45 in particular).

Given that the method would produce positive cell lines that secret anti-fVIII antibodies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain the antibodies taught by Jacquemin et al from animals by the `015 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because both methods would produce a reliable source of large amounts of monoclonal antibodies as taught by the `015 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claims 28-30 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacquemin et al (Blood. 1998 Jul 15;92(2):496-506) (IDS Ref) or U.S. Patent 5,744,446 each in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1).

Jacquemin *et al* teach the residues 2108-2121of the C1 domain (see page 498 1st col., under Recombinant DNA Fragments in particular). Jacquemin et al further teach that within the light chain of fVIII region there is a von Willebrand factor (vWF) binding site, which acts in conjuction with amino acid residues through 1689 in the A3 domain. Further Jacquemin et al teach that fVIII circulates complexed to vWF that protects fVIII from rapid degradation in plasma.

The `446 patent teaches antibodies specific for the C1 domain epitope can be isolated from total patient IgG by affinity chromatography wherein C1 is residues Arg2033-Asn2172 (see col., 19, lines 40-41 and col. 5, lines 55-56 in particular). The `446 patent teaches that the significance of this putative third epitope is unknown, but it appears to account for a minor fraction of the epitope reactivity in factor VIII (see col.17 lines 16-19 in particular).

The claimed invention differs from the reference teachings only by the recitation of a monoclonal antibody being able to recognize an epitope located in the C1 domain of factor VIII.

Campbell teaches that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (see page 3 figure 11.1 in particular). One field of research in which monoclonal antibodies may prove of particular value is in the study of chromosomal proteins. The search for those chromosomal proteins which are responsible for determining cell phenotype has been particularly long and comparatively fruitless and monoclonal antibodies are ideal tools for the dissection of the complex mixture of proteins. As hybridoma production becomes a more routine laboratory technique (see page 29 and 30 under Basic research in particular).

Claims 32-33 are included because an antibody is the same antibody irrespective of how it is made.

Given the importance of LC fVIII region in binding to vWF to form a complex that protects fVIII from rapid degradation in plasma, and that C1 domain epitope accounts for a minor fraction of the epitope reactivity in factor VIII, it would have been obvious to one of ordinary skill in the art at the time the invention was made to to make a monoclonal antibody as taught by Campbell against the residues 2108-2121 of the C1 domain taught by the Jacquemin et al or agaisnt the Arg2033-Asn2172 taught by the ``446 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was customary at the time the invention was made to make monoclonals against any new macromolecule as taught by Campbell.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacquemin *et al* or U.S. Patent 5,744,446 each in view of in view of Alisa Campbell., as applied to claims 28-30 and 32-33 above, and further in view of U.S. Patent No. 6,210,675.

The teachings of Jacquemin *et al*, and Campbell references, have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition comprising a monoclonal antibody and an acceptable carrier in claims 35-36.

The '675 patent teaches antibodies and methods of producing monoclonal antibodies to a polypeptide (column 5, lines 5-47). Monoclonal antibodies against a polypeptide can be obtained by fusing cells of an immortalizing cell line with cells which produce antibody against the polypeptide, and culturing the fused immortalized cell line. Also, the '675 patent teaches that antibodies produced can be used in quality control testing of the polypeptide; purification of the polypeptide or lysate; epitope mapping, when labeled, as a conjugate in a competitive type assay; and for antibody detection (column 5, lines 6-13 in particular). Finally, the '675 patent teaches that the antibody is in solution (column 7, lines 58-62 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the antibody in a composition as taught by `675 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the composition antibodies produced can be used in quality control testing of the polypeptide; purification of the polypeptide or lysate; epitope mapping, when labeled, as a conjugate in a competitive type assay; and for antibody detection as taught by '675 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
May 14, 2004

Christina Chan
CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600